

REMARKS

Claims 23-34 were pending in the instant application. Claims 23-34 have been amended and new claims 35-40 have been added. Thus, upon entry of this Amendment, claims 23-40 are pending in the application. For the Examiner's convenience, a copy of the claims as pending after the amendments herein is provided as Appendix A.

Claims 23-34 have been amended to recite "non-human animal". Support for these amendments may be found in the specification at least at page 18, lines 17-23 and page 34, lines 15-19. Claim 23 has also been amended to correct for a typographical error (omission of the phrase "is a"), as requested by the Examiner. New claims 35-40 have been added. Support for the new claims can be found in the claims as originally filed and throughout the specification, including at least at page 11, lines 1-2 and page 42, lines 1-4.

The Examiner has objected to the drawings because they include references not mentioned in the description. Applicants have amended the specification and drawings accordingly so that the numbering corresponds. Applicants submit herewith a replacement copy of Figures 4, 5, 9, and 10 which have been amended to include mention of the appropriate SEQ ID NO and to correct the numbering. A "Version With Markings to Show Changes Made" is attached herewith.

No new matter has been added. Applicants request that the amendments to the specification and claims be entered. Amendment of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and was done solely to more particularly point out and distinctly claim Applicants' invention in order to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Response to Restriction Requirement

The Examiner has required restriction to one of the following inventions under 35 U.S.C. § 121:

- I. Claims 23-34, drawn to transgenic organisms, wherein the transgenic organisms are non-human animals.
- II. Claims 23-34, drawn to transgenic organisms, wherein the transgenic organisms are plants.

In a phone conversation with the Examiner on September 30, 2002, Applicants attorney elected group I with respect to transgenic non-human animals. Applicants hereby affirm election of Group I.

Rejection of Claims 23-32 Under 35 U.S.C. § 101

The Examiner has rejected claims 23-32 under 35 U.S.C. § 101 as being directed to non-statutory subject matter. Claims 23-32 have been amended to specify transgenic non-human animals. Thus, Applicants respectfully request that the rejection under 35 U.S.C. § 101 be withdrawn.

Rejection of Claims 23-32 Under 35 U.S.C. §112, First ParagraphRejection of Claims 23-32 Under 35 U.S.C. §112, First Paragraph

Claims 23-32 have been rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. The Examiner states that while the specification is enabling with regard to a transgenic mouse, the specification "does not reasonably provide enablement for all other transgenic organisms embraced by the claims." The Examiner is of the opinion that Applicants have failed to enable transgenic non-human animals with their corresponding phenotypes, and further that "the specification fails to even disclose any particular type of

phenotype exhibited by a transgenic non-human animal of the invention." Applicants respectfully traverse this rejection.

As amended, claim 23 is directed to a transgenic non-human animal having a transgene integrated into the genome of the non-human animal and also having a *tet* operator-linked gene in the genome of the organism. The transgene of claim 23 comprises a transcriptional regulatory element functional in cells of the non-human animal operatively linked to a polynucleotide sequence encoding a fusion protein which activates transcription of said *tet* operator linked gene, wherein the fusion protein comprises a first polypeptide which is a Tet repressor operatively linked to a second polypeptide which directly or indirectly activates transcription in eukaryotic cells. The *tet* operator-linked gene of claim 23 further confers a detectable and functional phenotype on the non-human animal when expressed in its cells, wherein the transgene is expressed in cells of the non-human animal at a level sufficient to produce amounts of the fusion protein that are sufficient to activate transcription of the *tet* operator-linked gene, and in the absence of tetracycline or a tetracycline analogue in the non-human animal, said fusion protein binds to the *tet* operator-linked gene and activates transcription of the *tet* operator linked gene such that the *tet* operator-linked gene is expressed at a level sufficient to confer the detectable and functional phenotype on the organism, wherein the level of expression of the *tet* operator-linked gene can be downmodulated by administering tetracycline or a tetracycline analogue to the non-human animal.

As amended, claim 24 is directed to a transgenic non-human animal having a transgene integrated into the genome of the non-human animal, wherein the transgene comprises a transcriptional regulatory element functional in cells of the non-human animal operatively linked to a polynucleotide sequence encoding a fusion protein which activates transcription of a *tet* operator linked gene, the fusion protein comprising a first polypeptide which is a Tet repressor, operatively linked to a second polypeptide which

directly or indirectly activates transcription in eukaryotic cells, and said fusion protein is expressed in cells of the non-human animal. In addition, claims 33 and 34, which depend from claims 23 and 24 respectively, are directed to non-human animals selected from the group consisting of a mouse, a cow, a sheep, and a pig.

New claim 35 is drawn to a transgenic non-human animal selected from the group consisting of a mouse, a cow, a sheep, a goat, and a pig, having a transgene integrated into the genome of the non-human animal and also having a *tet* operator-linked gene in the genome of the organism, wherein the transgene comprises a transcriptional regulatory element functional in cells of the non-human animal operatively linked to a polynucleotide sequence encoding a fusion protein which activates transcription of said *tet* operator linked gene, the fusion protein comprises a first polypeptide which Tet repressor operatively linked to a second polypeptide which directly or indirectly activates transcription in eukaryotic cells, said *tet* operator-linked gene confers a detectable and functional phenotype on the organism when expressed in cells of the non-human animal, said transgene is expressed in cells of the non-human animal at a level sufficient to produce amounts of said fusion protein that are sufficient to activate transcription of the *tet* operator-linked gene, and in the absence of tetracycline or a tetracycline analogue in the non-human animal, said fusion protein binds to the *tet* operator-linked gene and activates transcription of the *tet* operator linked gene such that the *tet* operator-linked gene is expressed at a level sufficient to confer the detectable and functional phenotype on the organism, wherein the level of expression of the *tet* operator-linked gene can be downmodulated by administering tetracycline or a tetracycline analogue to the non-human animal.

New claim 36 is directed to a transgenic non-human animal selected from the group consisting of a mouse, a cow, a sheep, a goat, and a pig having a transgene integrated into the genome of the non-human animal, wherein the transgene comprises a

transcriptional regulatory element functional in cells of the non-human animal operatively linked to a polynucleotide sequence encoding a fusion protein which activates transcription of a *tet* operator linked gene, the fusion protein comprising a first polypeptide which is a Tet repressor, operatively linked to a second polypeptide which directly or indirectly activates transcription in eukaryotic cells, and said fusion protein is expressed in cells of the non-human animal.

The Examiner states that the claimed invention is not enabled because "the state of the art in transgenics is not a predictable art with respect to transgene behavior and the resulting phenotype." The claimed invention is directed to a transgenic non-human animal which has two transgenes integrated into its genome which comprise the tetracycline transcriptional activator (tTA) regulatory system (see page 12, lines 27-31 of the specification). The tTA system is a ***highly regulatable genetic system*** and has two components, a tet-operator linked gene of interest and a fusion protein which comprises a Tet repressor (TetR) fused to a transcriptional activator (see page 12, line 32 to page 14, line 16 of specification). Gene expression is regulated through the administration of tetracycline (Tc), or an analogue thereof, to the transgenic non-human animal. In the absence of Tc, the gene of interest, which is operatively linked to the tet operator, is expressed and results in a phenotype which depends entirely on the gene of interest.

Applicants provide a working example of a transgenic mouse which comprises the tTA regulatory system in Example 2 of the specification, wherein the gene of interest is the luciferase reporter gene. In Figure 14 and at pages 51-52 of the specification, Applicants demonstrate that transgenic mice carrying the tTA and luciferase linked tet operator gene have decreased or increased luciferase activity based on the presence or absence of Tc. Based on these results, Applicants show that the tTA regulatory system contained in the claimed transgenic non-human animal is a ***predictable system*** which provides a precise mechanism for controlling expression of a gene of interest. Applicants

submit that in contrast to the Examiner's assertions, the claimed transgenic non-human animals of the present invention are predictable with respect to transgene behavior and the resulting phenotype, by virtue of the demonstrated reliability of the tTA regulatory system.

The Examiner cites various references in support of his contention that "the state of the art of transgenics is not a predictable art with respect to transgene behavior and the resulting phenotype." These references are individually addressed below.

A. The Examiner states that there are many parameters, e.g. gene of interest, promoter, enhancer, coding, or non-coding sequences, in the transgene construct which must be considered in order to control transgene expression in the transgenic animal. In support of this notion, the Examiner cites Wall as stating, "'lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior.'" Wall provides a review of the progress being made in the field of transgenic livestock. Applicants assert that the unpredictability problem which is purported by Wall (as cited on page 61 by the Examiner) is solved by the non-human transgenic animals of the instant invention. Wall states that the unpredictability of transgene expression is partly attributable to the "position effect," wherein the expression of a transgene relies upon the transcriptional environment where it integrates. The claimed transgenic non-human animals contain their own transcriptional regulatory system, and therefore do not rely upon the neighboring DNA to control their expression. In the claimed non-human transgenic animals of the present invention, the gene of interest is only expressed in the presence of Tc - thus, eliminating the unpredictability of when the gene of interest would or would not be expressed.

B. The Examiner also cites Houdebine as disclosing that, "constructs must be designed case by case without general rules to obtain good expression of a transgene." Applicants assert that the example cited in Houdebine by the Examiner is limited to certain transgenes which were tested and is not a general statement regarding the field of transgenics as suggested by the Examiner.

Houdebine discusses the use of transgenic animals as a source of production of therapeutic products, and describes which animals and biological fluids are best for purification. Houdebine summarizes a number of experiments (pages 273-274) which involved creating transgenic animals, including mice and pigs, to produce a transgene product in their milk. In particular, Houdebine describes results from fusing "foreign cDNA" to milk regulatory regions, i.e. β -lactoglobulin gene promoter. After reviewing the results from these experiments, Houdebine states that "[f]rom the data, it is difficult to draw clear general rules to construct efficient vectors for expression of foreign genes in milk. Most likely, the regulatory regions from the various genes are not of equal potency." Houdebine concludes at page 274, 2nd column, as highlighted by the Examiner, that "[a]s a general rule, the regulatory elements involved in the control of milk protein gene expression are still far from being known in detail. The gene constructs using these promoters are therefore still done empirically, leading to unpredictable success and failure." Applicants respectfully submit that the Examiner's reference to Houdebine in regard to the assertion that transgenic constructs must be designed on a case by case basis was taken out of context. Houdebine describes challenges attributed to attaining gene expression as a product in the milk of a transgenic organism. Furthermore, the problems discussed by Houdebine are actually met by the Applicants' invention, as the claimed transgenic organisms have a controllable system

which is regulated by an exogenous effector molecule and does not rely on endogenous gene sequences.

C. The Examiner next cites Hammer *et al.* and Ebert *et al.* in support of the "unpredictability" in making transgenic animals. The Examiner relies on these references for teaching "transgene expression in different species of transgenic non-human animals is not predictable and varies according to the particular host species and specific promoter/gene combination." In particular, the Examiner states that Hammer teaches that "only transgenic mice exhibited an increase in growth due to the expression of the gene encoding human growth hormone."

Hammer teaches the production by microinjection of transgenic rabbits, sheep and pigs expressing *human* growth hormone under control of the *mouse* metallothionein-I promoter. The results show that the transgene integrated into the genome of each organism, with expression occurring in a significant proportion of each of the founder lines. The successes described in Hammer directly contradict the Examiner's assertion that producing transgenic non-human animals is unpredictable. Hammer demonstrates that the same construct can be inserted into a range of animals with successful expression of the transgene.

The Examiner suggests that the difference in the resulting phenotype between the transgenic mouse and pig is evidence that the transgene construct "did not cause the same phenotypic effect." As described in Hammer, the different phenotypes observed between the transgenic pig and mouse were attributable to the nature of the chosen transgene, i.e. the *human* growth hormone. To address this issue, Hammer states that, "introducing the porcine GH gene into pigs under the control of the mouse or human MT promoter or an alternative promoter may provide sufficient plasma pGH levels to enhance growth." The fact that Hammer observed a different phenotype in transgenic mice versus pigs when the

identical construct was used, simply indicates that a transgene designed for one species may not be optimal in another species. One of ordinary skill in the art would know that expression vectors should be designed with the particular host cell in mind. Furthermore, various promoters for expression in different species of host cells were known in the art. In sum, Applicants conclude that the difference in the phenotypes observed between the mouse and the pig carrying the same transgene is due to the nature of the transgene, i.e. it was biologically inactive, and that the intended phenotype would be observed in the pig with a functioning GH transgene.

Ebert teaches a transgenic pig which contains a transgene composed of a viral promoter (the MLV promoter) fused to rat somatotropin (rGH). Contrary to the Examiner's assertion, the results described in Ebert demonstrate that the transgene conferred a detectable phenotype. While the expression of the transgene did not cause an increased growth rate, the transgene did cause increased skeletal growth and reduced fat deposition, as well as elevated blood glucose levels.

Applicants submit that each of these references demonstrates the efficacy of the methodologies taught in the instant specification in the production of transgenic animals. It is therefore clear from the teachings of these references, that the methodologies taught by Applicants are equally valid for the production of non-murine transgenic animals expressing Tet repressor-transcriptional inhibitor fusion proteins.

D. As described by the Examiner, Mullins states that, "a given construct may react very differently from one species to another." Applicants submit that, as taught in the specification, a *construct, including the vector and gene of interest, as well as other elements, for example, a promoter, 5' and 3' flanking DNA of the gene of interest, etc., must be chosen according to the species for which it is intended* (see page 11, lines 3-5 and 22-28, at page 16, lines 30-36, at page 19, lines 17-21, and at page 15, lines 14-20).

In fact this notion is re-affirmed in the complete citation from Mullins from which the Examiner quoted, "***The use of nonmurine species for transgenesis will continue to reflect the suitability of a particular species for the specific questions being addressed.***" bearing in mind that a given construct may react very differently from one species to another." Applicants submit that one of ordinary skill in the art would recognize that certain constructs are designed for certain non-human animals, and that this construct may not be appropriate for other types of non-human animals, depending on the transgene, i.e. the gene of interest.

E. Kappel is cited by the Examiner as disclosing, "the existence of inherent cellular mechanisms that may alter the pattern of gene expression such as DNA imprinting." One of ordinary skill in the art would know to minimize possible complications from known cellular mechanisms, including DNA methylation. In the example chosen by the Examiner, one of ordinary skill would know to search the transgene construct for possible CpG methylation sites in order to reduce the chance that the transgene will be silenced due to methylation. Applicants also teach in the specification (see page 16, line 37 to page 17, line 29) that the transgene can be targeted to a specified region of the non-human animal's genome using homologous recombination. Thus, one of ordinary skill in the art would recognize that the transgene could be targeted to a chromosome region which is not considered to be an area of increased methylation.

F. The Examiner cites Strojek and Wagner in support of the notion that "a high degree of expression of a transgene in a mouse is often not predictive of high expression in other species...because, for example, the cis acting elements may interact with different trans-acting factors in these other species." Applicants submit that the claimed transgenic non-human animals actually address and solve this problem. In the transgenic non-

human animals of the invention, gene expression is completely based on a foreign gene regulatory system, and does not rely on endogenous factors to activate or inhibit gene expression. The transgenic non-human animals of the invention feature a system for regulating gene expression of eucaryotic genes using components of the Tet repressor/operator/inducer system of prokaryotes. Thus, Applicants therefore submit that the problem presented by the Strojek and Wagner reference is solved by the claimed invention.

In addition, Applicants note that the Strojek and Wagner reference cited by the Examiner actually demonstrates that technologies for successfully making transgenic non-human animals in non-mouse species were available in the art at the time filing the priority application (Strojek and Wagner was published in 1988). As summarized on page 233, transgenic rabbits, sheep, pigs, and chicken were described in the literature. Strojek and Wagner therefore actually supports Applicants' position that techniques for producing non-human transgenic animals other than mice were known in the art at the time of filing the priority application.

In further response to the Examiner's concern regarding the unpredictability of the instant invention, Applicants submit that the teachings in the instant specification with regard to the construction and use of the Tet repressor-transcriptional inhibitor fusion proteins have been successfully applied in a variety of eukaryotic cell types. Applicants refer the Examiner to:

- 1) Agarwal *et al.* (1995) *Proc. Natl. Acad. Sci. USA* 92:8493-8497, which uses the tTA system in human fibroblasts (see ref. BA in IDS);
- 2) Bergman *et al.* (1995) *Mol. Cell Biol.* 15:711-722, which uses the tTA system in HeLa cells (see ref. BH in IDS);

- 3) Buckbinder *et al.* (1994) *Proc. Natl. Acad. Sci. USA* 91:10640-10644, which uses the tTA system in human osteosarcoma cells (see ref. BO in IDS);
- 4) Cayrol and Flemington (1995) *J. Virol.* 69:4206-4212, which uses the tTA system in epithelial cells (see ref. CA in IDS);
- 5) Chen *et al.* (1995) *Cancer Research* 55:4536-4539, which uses the tTA system in colon carcinoma and prostate carcinoma cells (see ref. cb in IDS);
- 6) Gjetting *et al.* (1995) *Biol. Chem. Hoppe-Seyler* 376:441-446, which uses the tTA system in mammary carcinoma cells (see ref. DK in IDS);
- 7) Haase *et al.* (1994) *Mol. Cell. Biol.* 14:2516-2524, which uses the tTA system in human embryonic kidney fibroblasts (see ref. EB in IDS);
- 8) Howe *et al.* (1995) *J. Biol. Chem.* 270:14168-14174, which uses the tTA system in rat pituitary-derived cells (see ref. EI in IDS);
- 9) Miller and Rizzino (1995) *Exp. Cell Res.* 218:144-150, which uses the tTA system in embryonic carcinoma cells (see ref. FG in IDS);
- 10) Resnitzky *et al.* (1994) *Mol. Cell. Biol.* 14:1669-1679, which uses the tTA system in Rat-1 fibroblasts (see ref. FR in IDS);
- 11) Sopher *et al.* (1994) *Mol. Brain Res.* 26:207-217, which uses the tTA system in human neuroblastoma cells (see ref. GH in IDS); and
- 12) Wu *et al.* (1995) *Genes Dev.* 9:2350-2363, which uses the tTA system in NIH-3T3 cells (see ref. HC in IDS).

The fact that Tet repressor-transcriptional activator fusion proteins have been demonstrated to regulate target gene expression in a tetracycline-controlled fashion in a variety of cell types when constructed and used in accordance with the teachings of the instant specification indicates that the specification fully enables the construction and use of the Tet repressor-inhibitor fusion proteins of the invention in a variety of eukaryotic cells.

Furthermore, at the time of filing the priority application, the teachings of the specification with regard to the construction of transgenic organisms (see e.g., page 11), had been utilized by many groups in the production of a variety of transgenic organisms, including rats, pigs, sheep, and cows. Applicants refer the Examiner to examples of transgenic animals which were described in the literature at the time of filing the priority application :

- 1) Pursel et al. (*J. Reprod. Fertil. Suppl.* 41: 77-87, 1990; attached as Appendix B), which teaches the production by microinjection of transgenic pigs expressing bovine and human growth hormone under control of the mouse metallothionein-I promoter;
- 2) Rexroad et al. (*J. Anim. Sci.* 69: 2995, 1991; attached as Appendix C), which teaches the production by microinjection of transgenic sheep expressing bovine growth hormone or human growth hormone-releasing factor under the control of the mouse transferrin promoter or the mouse albumin promoter, respectively; and
- 3) Ebert et al. (*Bio/Technology* 9: 835, 1991; attached as Appendix D), which teaches the production by microinjection of transgenic goats expressing longer acting tissue plasminogen activator under the control of the murine whey acid promoter.

Each of these references demonstrates the efficacy of the methodologies taught in the instant specification in the production of transgenic animals. It is therefore clear from the teachings of these references that the methodologies taught by Applicants are valid for the production of non-murine animals transgenic for the Tet repressor-transcriptional inhibitor fusion proteins of the invention.

Rejection of Claims 27-30 Under 35 U.S.C. §112, First Paragraph

The Examiner also rejects claims 27-30 for "requir[ing] the use of embryonic stem (ES) cells for the production of the claimed transgenic non-human animal," although, according to the Examiner, ES cells are only available for the production of

transgenic mice. The Examiner cites Moreadith, Seamark, and Mullins in support of the assertion that ES cell technology is limited to mice. Applicants respectfully traverse this rejection.

Claims 27 and 28 specify that the transgene of the non-human transgenic animal is integrated at a predetermined location in the genome of the non-human animal. Claims 29 and 30 specify that the transgene of the non-human animal is integrated at a predetermined location such that expression of the fusion protein is controlled by 5' regulatory elements of an endogenous gene of the non-human animal and expression of the endogenous gene is controlled by at least one tet operator sequence.

The specification describes how to prepare transgenic organisms by homologous recombination such that the transgene is integrated at a predetermined location in the genome. Guidance is provided regarding the vectors required for homologous recombination (see e.g., pages 19-24 and 28-29). For example, in a preferred embodiment, the vectors contain the DNA encoding the fusion protein flanked at its 5' and 3' ends with additional nucleic acids corresponding to the eukaryotic gene at which homologous recombination is to occur, and can readily be prepared using standard molecular biology techniques known to those skilled in the art. Additionally, the specification cites, and incorporates by reference, several references describing homologous recombination methodologies (see e.g., page 19, line 37 to page 20, line 2), stating that these methodologies are well established in the art.

Moreover, at the time of the invention, the use of homologous recombination for site specific transgene integration had been successfully demonstrated in a number of organisms. Such examples are described in Moreadith, which states that, "putative pluripotent ES cell lines have been derived in a number of...species including hamster, pig, sheep, cattle, rabbit, rat, mink, monkey and even humans" (see page 214 "Summary"). Applicants also submit herewith as Appendix E, Sun et al. (1995) *Mol.*

Mar. Biol. Biotechnol. 4:193-9 (abstract), which describes pluripotent ES cells in zebrafish. Other examples of organisms in which homologous recombination has been successfully used include yeast, *Dictyostelium*, *Xenopus* and *Caenorhabditis elegans*. Applicants further submit the following representative examples of articles describing homologous recombination in these species, wherein the transgene is integrated into an animal's genome:

- 1) Compton et al. (1982) *Mol. Gen Genet.* 188:44-50, which describes the insertion of nonhomologous DNA into the yeast genome mediated by homologous recombination with a cotransforming plasmid (attached as Appendix F);
- 2) DeLozanne and Spudich (1987) *Science* 236:1086-1091, which describes site-specific disruption of a gene in *Dictyostelium* by homologous recombination (attached as Appendix G);
- 3) Carroll et al. (1986) *Mol. Cell. Biol.* 6:2053-2061, which describes homologous recombination of linear DNA substrates injected into *Xenopus* oocytes (attached as Appendix H); and
- 4) Broverman et al. (1993) *Proc. Natl. Acad. Sci. USA* 90:4359-4363, which describes alteration of *Caenorhabditis elegans* gene expression by targeted transformation via homologous recombination (attached as Appendix I); and
- 5) Bello et al. (1998) *Development* 125:2193-2202, which describes gene expression using the claimed tet regulatory system in insects (*Drosophila*) using P-element mediated transformation (attached as Appendix J).

Furthermore, additional methods and citations for producing site specific integration of transgenes using enzyme-assisted site specific integration systems are provided in the specification. Examples of such enzyme-assisted site specific integration systems include the Cre-lox recombinase target system and the FLP recombinase-FRT

target system (see page 31, lines 1-9 of the specification). At the time of the invention, these integration systems had been used successfully in a variety of organisms.

Applicants note that the above described references are a small sample of several publications available in the art demonstrating the integration of genetic material into a specific location of an organism, including homologous recombination. These references demonstrate that, at the time of filing the priority application, DNA had been successfully integrated at a predetermined location in the genome of a broad range of organisms, other than through the use of ES cells, as asserted by the Examiner.

Moreover, the fact that some experimentation may be necessary to produce a transgenic non-human animal with a gene at a specific location, does not constitute a lack of enablement as long as the amount of experimentation is not unduly extensive. *Amgen Inc. v. Chugai Pharmaceutical Co., Ltd.*, 927 F.2d 1200, 1213 (CAFC 1991). A considerable amount of experimentation is permissible if it is merely routine, or if the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Wands* 8 USPQ2d 1400-1407, 1404 (CAFC, 1988). In view of the teachings in the specification and the general knowledge in the art, the specification has provided sufficient guidance to the ordinarily skilled artisan as to how to make and use the invention, without undue experimentation. Accordingly, the specification meets the enablement requirement and Applicants thus respectfully request that the rejection of claims 23-34 under U.S.C. § 112 first paragraph, be withdrawn.

Rejection of Claims 23-34 Under the Judicially Created Doctrine of Obviousness-Type Double-Patenting

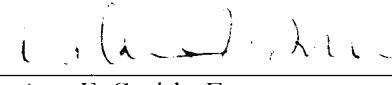
Claims 23-34 have been rejected under the judicially created doctrine of obviousness-type double patenting over U.S. Patent No. 5,859,301 (hereinafter '301). The Examiner states that while the claims are not identical, they both describe transgenic organisms "whose genomes comprise a transgene and a tet operator-linked gene." Applicants respectfully submit that '301 is not a co-invented or co-owned application and describes a process for preparing alkanone. Applicants therefore respectfully request that the rejection of claims 23-34 under the judicially created doctrine of obviousness-type double patenting over '301 be withdrawn.

CONCLUSION

In view of the foregoing remarks, reconsideration of the rejections and allowance of all pending claims is respectfully requested.

If a telephone conversation with Applicants' attorney would expedite the prosecution of the above-identified application, the examiner is urged to call Applicants' attorney at (617) 227-7400.

Respectfully submitted,
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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the specification:

Please replace the paragraph beginning at page 8, line 3, of the specification as follows:

(Amended) ---Fig. 9A-9C. [SEQ ID NO: 8] The polynucleotide sequence of the cDNA coding for the rabbit progesterone receptor under control of PhCMV*-l ---

Please replace the paragraph beginning at page 8, line 5, of the specification as follows:

(Amended) ---Fig. 10A-B. [SEQ ID NO: 9] The polynucleotide sequence of the cDNA coding for the rabbit progesterone receptor under control of PhCMV*-l ---

Please amend Figures 4, 5, 9, and 10 of the drawings as follows:

In the claims:

23. **(Amended)** A transgenic non-human animal organism having a transgene integrated into the genome of the non-human animal organism and also having a *tet* operator-linked gene in the genome of the organism, wherein:

the transgene comprises a transcriptional regulatory element functional in cells of the non-human animal organism operatively linked to a polynucleotide sequence encoding a fusion protein which activates transcription of said *tet* operator linked gene,

the fusion protein comprises a first polypeptide which is a Tet repressor operatively linked to a second polypeptide which directly or indirectly activates transcription in eukaryotic cells,

said *tet* operator-linked gene confers a detectable and functional phenotype on the non-human animal organism when expressed in cells of the non-human animal organism.

said transgene is expressed in cells of the non-human animal organism at a level sufficient to produce amounts of said fusion protein that are sufficient to activate transcription of the *tet* operator-linked gene; and

in the absence of tetracycline or a tetracycline analogue in the non-human animal organism, said fusion protein binds to the *tet* operator-linked gene and activates transcription of the *tet* operator linked gene such that the *tet* operator-linked gene is expressed at a level sufficient to confer the detectable and functional phenotype on the organism, wherein the level of expression of the *tet* operator-linked gene can be downmodulated by administering tetracycline or a tetracycline analogue to the non-human animal organism.

24. **(Amended)** A transgenic non-human animal organism having a transgene integrated into the genome of the non-human animal organism, wherein:

the transgene comprises a transcriptional regulatory element functional in cells of the non-human animal organism operatively linked to a polynucleotide sequence encoding a fusion protein which activates transcription of a *tet* operator linked gene,

the fusion protein comprising a first polypeptide which is a Tet repressor, operatively linked to a second polypeptide which directly or indirectly activates transcription in eukaryotic cells, and

said fusion protein is expressed in cells of the non-human animal organism.

25. **(Amended)** The non-human animal organism of claim 23, wherein the second polypeptide of the fusion protein comprises a transcription activation domain of herpes simplex virion protein 16.

26. **(Amended)** The non-human animal organism of claim 24, wherein the second polypeptide of the fusion protein comprises a transcription activation domain of herpes simplex virion protein 16.

27. **(Amended)** The non-human animal organism of claim 23, wherein the transgene is integrated at a predetermined location in the genome of the non-human animal organism.

28. **(Amended)** The non-human animal organism of claim 24, wherein the transgene is integrated at a predetermined location in the genome of the non-human animal organism.

29. **(Amended)** The non-human animal organism of claim 27, wherein the transgene is integrated at a predetermined location such that expression of the fusion protein is controlled by 5' regulatory elements of an endogenous gene of the non-human animal organism and expression of the endogenous gene is controlled by at least one *tet* operator sequence.

30. **(Amended)** The non-human animal organism of claim 28, wherein the transgene is integrated at a predetermined location such that expression of the fusion protein is controlled by 5' regulatory elements of an endogenous gene of the organism and expression of the endogenous gene is controlled by at least one *tet* operator sequence.

31. **(Amended)** The non-human animal organism of claim 23, wherein the *tet* operator-linked gene is a second transgene comprising a gene of interest operably linked to at least one *tet* operator sequence.

32. **(Amended)** The non-human animal organism of claim 24, wherein the *tet* operator-linked gene is an endogenous gene that has been operatively linked to at least one *tet* operator sequence.

33. **(Amended)** The non-human animal organism of claim 23, which is selected from the group consisting of: a mouse, a cow, a sheep, and a pig, and a plant.

34. **(Amended)** The non-human animal organism of claim 24, which is selected from the group consisting of: a mouse, a cow, a sheep, and a pig, and a plant.